Return of Elevated Blood Pressure after Withdrawal of Antihypertensive Drugs

By VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP ON ANTIHYPERTENSIVE AGENTS*

SUMMARY

The rate at which arterial pressure rises after discontinuing active treatment was investigated in a group of 86 hypertensive patients who received treatment with hydrochlorothiazide, reserpine and hydralazine for two years or longer and whose diastolic pressures averaged below 96 mm Hg for the last year of treatment. Sixty patients were assigned double-blind to placebos and 26 were continued on active drugs.

Forty-two of the placebo group of patients were removed over an 18 month follow-up because of return of elevated blood pressures, 39 being removed in the first six months. Six patients in the placebo group and none in the treated group were removed because of morbid events. Nine or 15% of the placebo patients remained normotensive. The rate of rise in arterial pressure in the placebo group appeared to be related directly to the height of the pressure prior to initiation of active treatment and inversely to the age of the patients.

Serum uric acid fell significantly while serum potassium rose significantly after active treatment was discontinued. The glucose tolerance test changed slightly in a direction toward normal while serum creatinine showed no significant change.

Additional Indexing Words:

Hypertension Placebo effects in hypertension Return of hypertension
Antihypertensive drug withdrawal

THAT RESETTING of blood pressure control mechanisms can occur is suggested by observations of McCubbin and his associates.[1] They demonstrated upward resetting of the baroreceptors in dogs subjected to experimental renovascular hypertension.

The available data in man on modification of hypertension following long term treatment with antihypertensive drugs are conflicting. Page and Dustan[2] initially reported that 9 of 27 patients in whom treatment had been discontinued remained essentially normotensive without drug therapy for periods varying from six months to five years of observation. In a later review of 65 patients, however, the same authors found that diastolic hypertension reappeared in all but two patients.[3] In general, the earliest to manifest return of the hypertension were the patients with malignant or with renal hypertension while the longest remissions were seen in the patients with essential hypertension.

Perry and his associates[4] were able to withdraw drug treatment in 16 or 5% of 316 severely hypertensive patients without inducing a rise in blood pressure. Eleven of these patients had benign essential hypertension and five originally had malignant hypertension. Remissions were more frequent among patients who had hydralazine toxicity during treatment.

Thurm and Smith[5] discontinued antihypertensive drugs in 69 patients. They found that 16 or 23% remained normotensive for periods of 10 to 42 months after discontinuing treatment. The patients with the mildest elevations of blood pressure and the least apparent vascular disease were the most apt to remain normotensive, but there was no correlation with the known duration of the hypertension or with the length of treatment. Unlike the previous investigators, Thurm and Smith concluded that long term remission of hypertension is not an infrequent occurrence in essential hypertensives treated with antihypertensive drugs.

The reason for the discrepant results reported by these various authors may reside in the type of hypertensive patients under study. Patients with severe hypertension were preponderant in the first two studies whereas Thurm and Smith investigated patients with mild and moderate hypertension.

From participating Veterans Administration hospitals in Washington, D.C.; West Haven, Conn.; Salt Lake City; Birmingham; Nashville; Jackson, Miss.; Iowa City; Brooklyn; Oklahoma City; Richmond; West Roxbury; Pittsburgh; San Juan, PR; St. Louis; Dayton; Memphis; Allen Park.

*For a complete list of the participants in this study, see the addendum at the end of the article.

Address for reprints: Edward D. Freis, M.D., Senior Medical Investigator, Veterans Administration Hospital, 50 Irving Street NW, Washington, D.C. 20422.

Received January 16, 1975; accepted for publication February 3, 1975.

Further studies seemed indicated in an attempt to resolve this question.

Materials and Methods

When the Veterans Administration Cooperative Study on morbidity[6] was terminated there were a number of treated patients whose blood pressures had been controlled at normotensive levels for a period of two years or longer. This group of patients was entered into the present study which was designed to re-examine the question of re-establishment of normal pressure in previously treated hypertensive patients.

The design of the original trial from which the 86 patients were drawn has been described in previous communications.[6, 7] The original trial, in which all of these 86 patients were assigned to the active treatment group, will be designated as trial A and the present trial, in which the effect of withdrawal of treatment was assessed, will be called trial B. In trial B the 86 patients were subdivided by stratified randomization so that 60 patients or 70% were assigned double-blind to placebos and 26 patients or 30% were continued on active medications. The latter treatment as in trial A consisted of hydrochlorothiazide, reserpine and hydralazine.[6]

All of the patients who entered trial A were male veterans with established hypertension. All were hospitalized prior to treatment. Their blood pressure was measured in the hospital at least three times daily for six days. The average of their readings of diastolic blood pressure from the fourth through the sixth day of hospitalization was 90 mm Hg or higher and the average of the diastolic blood pressures recorded in the outpatient clinic while receiving placebos before randomization into trial A ranged between 90 and 129 mm Hg. Twenty-seven patients exhibited initial diastolic blood pressures in the range of 115–129 mm Hg and 59 were in the range of 90–114 mm Hg prior to entering trial A. Forty-four patients entering trial B were black and 42 were white. Their average age was 52.2 years for the placebo group and 52.8 years for the treated patients at the time of randomization into trial B.

The characteristics of the patients prior to receiving any treatment, that is prior to entering trial A, are indicated in table 1. The average pressures taken during the last two outpatient visits preceding their randomization into trial A were 171/109 mm Hg for the 60 patients randomized onto placebos in trial B and 171/112 mm Hg for the 26 patients continued on active drugs. The average severity scores were not significantly different in the 60 placebo treated and 26 actively treated patients (table 1). The duration of known hypertension prior to any treatment was 6.3 years in the placebo group and 7.4 years in the actively treated patients. The average duration of active treatment prior to entering the present trial was 4.6 years for both groups. The blood pressure during the last year of treatment averaged 129/82 in the patients randomized to placebos and 124/80 mm Hg in the patients who continued on active treatment. All 86 patients had been on active treatment with good control for a minimum of two years prior to randomization.

Screening of patients for randomization into the present trial began on October 1, 1970. The first visit on or subsequent to this date was called the eligibility visit. To be eligible the patient had to meet the following criteria: 1) The diastolic blood pressures for the two preceding visits plus the eligibility visit averaged 90 mm Hg or less. 2) No diastolic blood pressures above 95 mm Hg were recorded during any of these three visits. 3) The average of all diastolic blood pressures during the preceding 12 months was 95 mm Hg or less.

Patients who had major cardiovascular complications in the past were excluded. These complications are defined in a prior report[7] and include stroke, myocardial infarction, congestive heart failure, renal failure and others. Also excluded were patients who exhibited violations of pill counts on more than two clinic visits during the preceding year. Patients who had been transferred to drugs other than the hydrochlorothiazide-reserpine-hydralazine combination used in the original morbidity trial also were excluded. All patients were informed that they may be transferred to inert tablets but they would be replaced on active treatment if the hypertension became re-established. Written informed consent was obtained in all cases.

Blood pressures were measured by the nurse or clinic assistant in the right arm using a mercury manometer after the patient had been resting supine in a separate examining room for 15 minutes. Both the point of muffling and of disappearance were recorded but only the values at disappearance are reported in this paper. Blood pressures then were recorded with the patient sitting and standing. Subsequently, blood pressure was measured in the right arm by the clinic physician in the sitting position only. The latter values form the basis for the present report.

The end point criteria for removing a patient from the trial following randomization were as follows: 1) One visit with diastolic levels above 129 mm Hg. 2) Any two visits with diastolic levels above 114 mm Hg. 3) Any three visits with diastolic levels above 104 mm Hg. 4) Any five visits with diastolic levels above 94 mm Hg. 5) Any major cardiovascular complication (class A or B morbid event or treatment failure).[7]

Patients were seen at 1, 3, 7, 11, 15, 19 and 23 weeks following randomization. At the end of the 23rd week the diastolic blood pressures recorded at all of these visits were averaged. If the average exceeded 89 mm Hg the patient was removed from the trial. Otherwise he continued in the study for an additional 12 month period unless his blood pressure rose to levels which met the criteria for termination as indicated above. The blood pressures taken during the first six month period following randomization were disregarded in making the decision to terminate. Pill counts were carried out throughout the trial.

Table 1

*Characteristics of Patients Prior to Entering Trial A**

Characteristic	Placebo group† (mean)	Active group† (mean)
Height (in.)	68.3	68.9
Weight (lb)	174.8	186.8
Duration known hypertension (yrs)	6.3	7.4
Average clinic systolic pressure (mm Hg)	171.0	171.0
Average clinic diastolic pressure (mm Hg)	108.8	111.6
Severity scores:		
Optic fundi (0–4)	1.1	1.1
Cardiac (0–4)	0.7	0.8
Central nervous system (0–4)	0.4	0.2
Renal (0–4)	0.3	0.6

*Trial A indicates original morbidity study.
†Indicates assignment in trial B (present study).

The effect of withdrawal of long term thiazide treatment on certain blood constituents also was determined. At the third week after randomization blood was drawn for fasting blood sugar, uric acid, serum potassium and creatinine. The patients were also given 100 grams of glucose orally and samples for blood sugar were drawn at 1, 2 and 3 hours thereafter to compare with the glucose tolerance tests carried out during active treatment in trial A.

Results

Changes in Blood Pressure

During the entire postrandomization follow-up period of 72 weeks, 51 of the 60 placebo treated patients were removed from the trial. Of this number 42 were terminated because of return of increased arterial pressures, six because of major cardiovascular complications and three for reasons unrelated to their blood pressure. Among the 26 actively treated patients there were no morbid events and only one patient was removed from the trial because of a gradually rising blood pressure.

Thirty-nine of the 42 placebo treated patients who were removed because of significant increase in blood pressure attained the criteria for termination from trial B within the first six months following randomization. During this period three patients met the terminating criterion of two clinic visits with diastolic levels above 114 mm Hg, 12 had three visits with diastolic pressures above 104 mm Hg and 16 patients had five visits with diastolic reading above 94 mm Hg. Six patients were removed because their diastolic blood pressure averaged 90 mm Hg or above during the initial six months following randomization. Two additional patients were removed after four visits because all of their diastolic readings were 98 mm Hg or higher and each had two diastolic readings of 109 or higher preceding termination. Because of this clear evidence of return of elevated pressures they were removed from the trial even though their readings did not fit any of the listed criteria required for termination.

The majority of the patients were removed during the second to sixth postrandomization month rather than earlier because the levels of diastolic elevation attained were only moderate; therefore, three to five clinic visits were needed to meet the criteria required for termination. At 23 weeks after randomization 78.9% of the placebo patients had exhibited at least two consecutive readings of diastolic blood pressure of 95 mm Hg or above (fig. 1). The 95% confidence limits at 23 weeks were 67.4% and 90.4% of the placebo group developing terminating criteria. Only three patients developed terminating blood pressure criteria after the first six months of follow-up (table 2). The terminating criterion in these latter patients was a diastolic blood pressure above 94 mm Hg on five of the clinic visits. They were removed after 11, 12 and 14 months respectively following randomization.

Nine or 15% of the patients in the placebo group as well as 21 of the 26 patients in the treated group remained in the trial until its termination at 72 weeks of follow-up. The nine remaining placebo treated patients had an average blood pressure of 153/102 mm Hg prior to their original treatment in trial A. The 48 patients who were removed from the study because of elevated blood pressure or cardiovascular complication had a higher average pretreatment blood pressure of 174/110 mm Hg. After 12 months of treatment the average blood pressure was 131/83 mm Hg in the nine patients who remained normotensive on placebos and 133/87 mm Hg in the 48 who returned to hypertensive levels or had a cardiovascular event.

Morbidity

As indicated above six patients in the placebo group developed a cardiovascular complication during the postrandomization period. No morbid event occurred in the smaller group of patients who remained on active drugs. However, the difference was not significant using the Chi square test. The six cardiovascular complications were fatal myocardial infarction in one, nonfatal congestive heart failure in three, atrial fibrillation in one and right bundle branch block in one patient.

Characteristics Associated with Rate of Return of Hypertension

The rate of increase in pressure also was analyzed using a more sensitive index then the termination criteria for estimating the re-establishment of elevated pressures. This index, which was called the

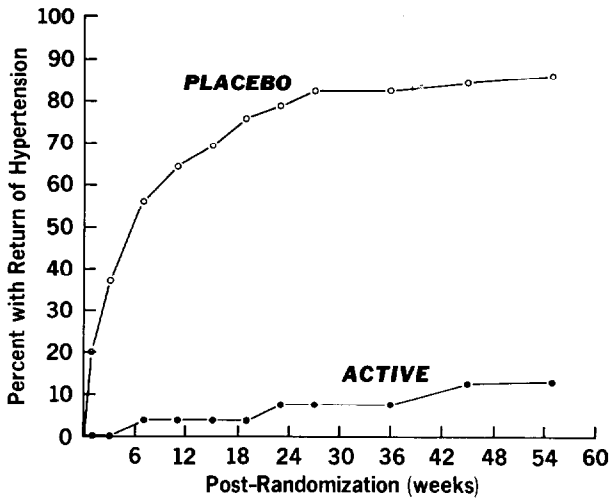

Figure 1

Cumulative percent of patients attaining diastolic blood pressure of 95 mm Hg or higher on two successive clinic visits ("2 × 95+") is shown on the ordinate. Time after randomization is shown on the abscissa. At six weeks after randomization 51% of the placebo group demonstrated "2 × 95+" and at six months 82% had reached this level.

Table 2

Terminating Events in Placebo Treated Patients

Time from randomization in weeks	Number of patients terminated				Cumulative percent terminated for cardiovascular causes
	Elevated blood pressure	Cardiovascular complications	Noncardiovascular reasons	Total	
1	0	0	0	0	0
3	2	0	1	3	3
7	9	1	0	10	20
11	9	0	0	9	36
15	2	3	0	5	44
19	6	1	1	8	57
23	11	0	0	11	76
27	0	0	0	0	76
36	0	0	0	0	76
45	1	0	0	1	78
54	1	0	0	1	79
63	1	0	1	2	82
72	0	1	0	1	84
Totals	42	6	3	51	84

"2 × 95+" criterion, indicated the time from randomization at which the diastolic blood pressure was 95 mm Hg or higher on two consecutive clinic visits. The percentage of patients reaching "2 × 95+" over time is shown in figure 1. The curve for the placebo group is seen to rise steeply initially and then more gradually in a roughly parabolic shape. At six weeks 51% of the patients had attained "2 × 95+" and at six months 82% had reached this level of blood pressure.

Various clinical features of the placebo group were examined in order to determine the characteristics which correlated with an early return of elevated pressure. Characteristics such as blood pressure and target organ damage (severity scores) prior to entering trial A were assessed with respect to the percentage of patients who attained "2 × 95+" return of hypertension three, 11 and 23 weeks after randomization in the present trial.

The most significant characteristic was the average clinic diastolic blood pressure prior to entrance into trial A, the median value of which was 107.5 mm Hg. Using a pretreatment average diastolic blood pressure of 108 mm Hg, 20% of patients below this level attained "2 × 95+" at three weeks as opposed to 55% of the group with initial diastolic pressure of 108 or higher (table 3). Using a one-tailed Chi-square test the difference was significant at all of the postrandomization periods examined with $P < 0.01$ at three weeks, $P < 0.005$ at 11 weeks and $P < 0.05$ at 23 weeks. The correlation between pretreatment diastolic blood pressure and the average of the readings at 19 and 23 weeks after withdrawing treatment is shown in figure 2. If the patient was withdrawn from the study prior to that time the diastolic blood pressures taken on the last two visits prior to withdrawal were used to determine the average reading. The patients with higher pretreatment diastolic blood pressures also had greater blood pressure increases after withdrawing treatment ($r = .42$).

With respect to pretreatment average clinic systolic blood pressure, the patients with systolic levels of 167 mm Hg or higher showed a greater return to "2 × 95+" than those with lower systolic readings. However, the difference was only significant ($P < 0.05$) at the 11th week postrandomization and not at three or 23 weeks.

Significantly elevated pressures returned more quickly in black patients than in white and in patients under age 50 as opposed to those age 50 and above

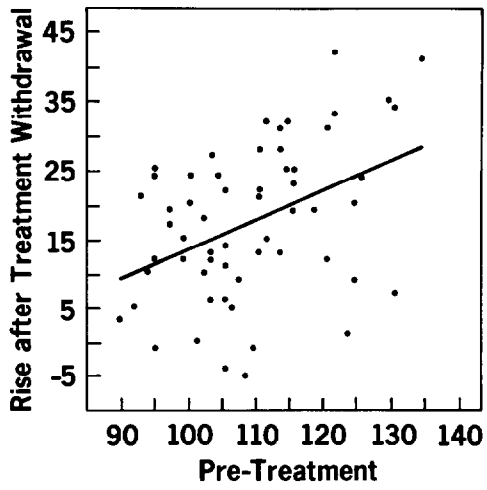

Figure 2

Change in diastolic blood pressure after discontinuation of treatment is shown on the ordinate. Level of diastolic blood pressure prior to beginning treatment in trial A is indicated on the abscissa. The degree of rise after discontinuing active drugs is correlated with the level of pretreatment diastolic blood pressure.

Table 3

Relationship of Various Characteristics to Rate of Return of Elevated Blood Pressure

Characteristic	No. of patients	Percent of placebo patients reaching "2× 95+" by following week after randomization		
		3	11	23
Age (yrs)				
≤ 49	25	54	71	82
50+	35	26	60	77
Race				
White	30	24	59	70
Black	30	50	70	87
Duration known hypertension				
< 5 yrs	34	32	65	79
5+ yrs	26	44	64	79
Average clinic systolic blood pressure (mm Hg) (pretreatment)				
≤ 166	31	29	52	72
167+	29	46	79	86
Average clinic diastolic blood pressure (mm Hg) (pretreatment)				
≤ 107	30	20	47	68
108+	30	55	83	90
Total severity score (pretreatment)				
2 – 7	39	42	68	83
8 – 15	21	29	57	71
Duration of treatment (yr)				
2 – 3.9	23	48	78	83
4 – 7	37	31	56	77
Average systolic level for last year of treatment (mm Hg)				
≤ 126	31	39	65	86
127+	29	36	64	71
Average diastolic level for last year of treatment (mm Hg)				
≤ 82	34	35	62	81
83+	26	40	68	76

(table 3). The differences were significant ($P < 0.05$) at the third week following withdrawal of active treatment but not at the 11th or 23rd weeks. The racial difference probably was not associated with race, *per se*, but rather with the level of the pretreatment diastolic blood pressure which was higher in the black patients. The diastolic blood pressures of the black patients prior to entering into trial A averaged 112 mm Hg, whereas those of the white patients averaged only 106 mm Hg. The difference was significant ($P < 0.025$). No correlation was found, however, between age and pretreatment blood pressure. The correlation coefficient was $r = -0.12$. Therefore, age, *per se*, appeared to have some influence on the rate of return of elevated pressures, in that the younger the age the greater the tendency for the high pressures to become re-established after withdrawal of treatment regardless of pretreatment level of blood pressure.

Those who exhibited a fall of 20 mm Hg or more after treatment in trial A exhibited a significantly ($P < 0.05$) greater return to "2 × 95 + " at three weeks following withdrawal of treatment than those who exhibited lesser falls of diastolic pressure during trial A. This result, however, probably is associated with the fact that those with the highest blood pressures prior to randomization showed the greatest falls after treatment in trial A. This result is shown in figure 3 which displays the relationship between pretreatment diastolic blood pressure and the degree of fall at the eighth month following the beginning of treatment. The two were strongly correlated ($r = 0.72$).

Changes in Blood Chemistries

The changes in serum uric acid, potassium and creatinine three weeks after randomization into trial B

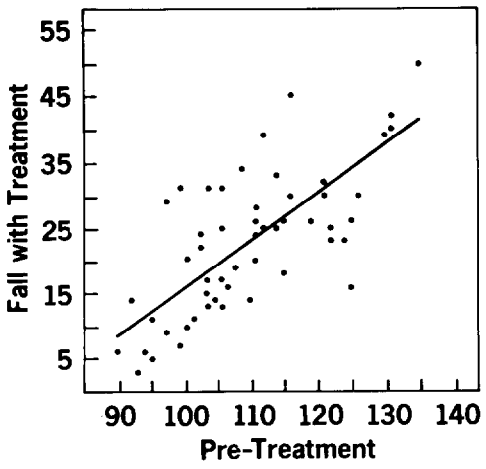

Figure 3

Level of diastolic blood pressure prior to treatment in trial A is shown on the abscissa. The subsequent fall with treatment is indicated on the ordinate. The two are strongly correlated (r = 0.72).

are shown in table 4. Comparison was made with the values obtained at the last annual examination in trial A, while all patients were undergoing active treatment prior to randomization into trial B. Uric acid values were obtained on 51 of the 60 patients who were assigned to placebos and on 24 of the 26 patients who were continued on active treatment. Serum uric acid fell significantly ($P < .0005$) in the placebo group from a mean of 7.5 to 6.5 mg/100 ml. Serum potassium rose significantly ($P < .0005$) after withdrawal of active treatment from a mean value of 3.7 mEq/L to 4.2 mEq/L. Neither serum uric acid nor serum potassium changed significantly in the patients who continued on active treatment. Serum creatinine did not change significantly in either the placebo or actively treated groups of patients.

Glucose tolerance tests were available in 51 of the 60 patients transferred to placebos and in 22 of the 26 patients continued on active treatment. These patients were not prepared with special diets prior to the glucose tolerance tests. The results obtained three weeks after randomization were somewhat inconclusive (table 5). There were no significant changes in the actively treated patients. In the placebo group there were significant falls ($P < 0.05$) in the fasting and three hour values but not in the one and two hour values or in the sum of the fasting through three hour values.

Discussion

Following substitution of placebos, significantly elevated blood pressure reappeared only gradually in the majority of patients. Using two successive clinic visit readings of 95 mm Hg or higher as the criterion for re-establishment of hypertension, 37% of patients receiving placebos met this criterion three weeks after treatment was stopped, 66% at 12 weeks, and 86% at one year. However, nine percent of the patients remained normotensive for the entire one and one-half years of observation.

These results are intermediate between those reported by Thurm and Smith[5] and the findings observed by others.[3, 4] Thurm and Smith observed a gradual return of hypertension in the majority of their patients while 23% maintained normal blood pressures for 10 to 42 months after discontinuing active treatment. On the other hand, Dustan and associates[3] and Perry and his coworkers,[4] who observed primarily patients with severe hypertension, usually found a rapid return of the elevated blood pressure and only a small percentage of patients remaining normotensive.

The present observations indicate that arterial pressure is capable of modification following long term treatment. Were this not the case the elevated pressures would reappear promptly, whereas in most patients its re-establishment was delayed over periods of weeks and months. Nevertheless, in the majority of cases the elevated pressures eventually returned indicating that the modification is not permanent except possibly in a few. What the factors may be that eventually cause the arterial pressure to increase are not clear from this study. A similar fall and gradual return of hypertension also may be seen after a major complication such as myocardial infarction or cerebral vascular accident or after major surgery.

A search was made for parameters that might be influential in determining the rate at which the arterial

Table 4

Changes in Serum Potassium, Uric Acid and Creatinine Three Weeks after Entering Trial B

Measurement	Placebo group				Active drug group			
	No.	Mean in trial A	Mean in trial B	P*	No.	Mean in trial A	Mean in trial B	P*
Potassium (mEq/L)	45	3.7	4.2	<.0005	22	3.8	3.8	NS
Uric acid (mg/100 ml)	51	7.5	6.5	<.0005	24	7.2	7.2	NS
Creatinine (mg/100 ml)	50	1.30	1.27	NS	23	1.39	1.33	NS

*Student's *t*-test was calculated to test the significance of the difference between means for paired observations. The *P* value was determined using a one-tailed test. NS indicates not significant.

Table 5

Changes in Glucose Tolerance Test Three Weeks after Entering Trial B

Blood glucose (mg/100 ml)	Placebo group				Active drug group			
	No.	Mean in trial A	Mean in trial B	*P*	No.	Mean in trial A	Mean in trial B	*P*
Fasting	51	112	105	<.05	24	112	113	NS
1 hr after glucose	51	184	187	NS	23	168	177	NS
2 hr	51	171	159	NS	23	148	148	NS
3 hr	51	141	122	<.05	22	119	114	NS
Sum of values	51	608	573	NS	22	534	546	NS

pressure increases and for the characteristics that lead to a sustained normalization of the blood pressure despite withdrawal of treatment. The most impressive correlation with the rate of increase in arterial pressure was the level of pretreatment blood pressure, particularly the diastolic pressure. The correlation was direct; the higher the level of pressure before instituting treatment, the more quickly in general was the pretreatment pressure re-established after discontinuing treatment. The patients who remained normotensive throughout the one and one-half years of follow-up came from the group who had the mildest severity of hypertension prior to treatment.

The other parameter which correlated with the rate of increase in pressure was age. The blood pressure of younger patients tended to rise more quickly to hypertensive levels than that of older patients irrespective of the level of blood pressure. Other parameters which appeared to correlate with the rate of increase in pressure could be explained by the fact that pretreatment levels of blood pressure tended to average higher in certain groups of patients. For example, black patients exhibited an earlier increase in pressure than whites but their pretreatment blood pressures also averaged significantly higher. The same explanation pertains to the observed direct correlation between degree of blood pressure reduction with treatment and rate of increase in pressure following discontinuation of treatment. The patients showing the greatest fall in blood pressure with treatment were those with the highest pretreatment levels of blood pressure. Level of pretreatment blood pressure and age, therefore, remain as the only primary correlates with the rate of return of increased pressure.

It should be emphasized that all of the patients had established hypertension since patients with borderline hypertension whose diastolic blood pressures fell to normal during hospitalization were excluded. If such borderline hypertensive patients had been included in the trial it is possible that a higher percentage of patients would have remained normotensive during the follow-up period.

The changes in blood chemistry values following withdrawal of treatment can be accounted for by the effect of withdrawing treatment with hydrochlorothiazide. Serum uric acid fell significantly, serum potassium rose significantly and glucose tolerance tended to return toward normal. There was no significant change in serum creatinine indicating that in this group of patients with normal or nearly normal renal function there was no evidence of depression of renal function as judged by serum creatinine values during the period of reduced blood pressure.

Addendum

Members of Study Group: Edward D. Freis, MD, Chairman: Massimo Calabresi, MD; C. Hilmon Castle, MD; Eugene C. Clark, MD; William S. Coppage, Jr., MD; Leo Elson, MD; Annette Fitz, MD; Rudph E. Fremont, MD; Edward D. Frohlich, MD; Arthur S. Gear, MD; David Littman, MD; Donald McCaughan, MD; Milos Ulrych, MD; Eli A. Ramirez, MD; H. Mitchell Perry, Jr., MD; James T. Taguchi, MD; J. R. Thomas, MD; Frederick N. Talmers, MD.

Consultants and Associates: Walter M. Kirkendall, MD; David W. Richardson, MD; Harold W. Schnaper, MD; Paul D. Williams, M.S.; Lawrence W. Shaw, A.M.; Mary C. Kyle, M.S.; Bert Silverman.

References

1. McCubbin JW, Green JH, Page IH: Baroreceptor function in chronic renal hypertension. Circ Res **4:** 205, 1956
2. Page IH, Dustan HP: Persistence of normal blood pressure after discontinuing treatment in hypertensive patients. Circulation **25:** 433, 1962
3. Dustan HP, Page IH, Tarazi RC, Frohlich ED: Arterial pressure responses to discontinuing antihypertensive drugs. Circulation **37:** 370, 1968
4. Perry HM Jr, Schroeder HA, Catanzaro FJ: Studies on the control of hypertension. VIII. Mortality, morbidity and remissions during twelve years of intensive therapy. Circulation **33:** 958, 1966
5. Thurm RH, Smith WM: On resetting of "barostats" in hypertensive patients. JAMA **201:** 301, 1967
6. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. I. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA **202:** 1028, 1967
7. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA **213:** 1143, 1970